KEY PAPER EVALUATION

Is there enough evidence with evolocumab and alirocumab (antibodies to proprotein convertase substilisin-kexin type, PCSK9) on cardiovascular outcomes to use them widely?

Evaluation of Sabatine MS, Giugliano RP, Wiviott SD et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med 2015;372:1500-1509, and Robinson JG, Farnier M, Krempf M et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 2015;372:1488-99.

Abstract

Introduction: Statins alone often do not reduce LDL cholesterol levels sufficiently to given maximum cardiovascular benefit. Thus, additional drugs are required to reduce the levels of LDL cholesterol. Monoclonal antibodies to PCSK9 have recently been shown to decrease LDL cholesterol, but it is not known whether they improve cardiovascular outcomes.

Areas covered: Evaluation of two clinical trials reporting cardiovascular outcomes with antibodies to PCSK9; the OSLER extension with evolocumab and the ODYSSEY LONG TERM trial with alirocumab.

Expert opinion: In OSLER and ODYSSEY LONG TERM, there were very few cardiovascular outcomes, but the trials do suggest that evolocumab and alirocumab may reduce these outcomes. However, there are also some safety concerns with both of these antibodies. Large clinical outcome trials are underway with both evolocumab and alirocumab, which will probably clarify both the safety concerns and any cardiovascular benefits with these antibodies. In our opinion, these antibodies may be suitable for use in subjects with familial hypercholesterolemia, who are uncontrolled with their present medications, provided intensive safety and cardiovascular monitoring is being undertaken. However, evolocumab and alirocumab should be used with caution in other subjects, until outcome studies in higher numbers of subjects, have shown acceptable safety and cardiovascular profiles.

Key words alirocumab, cardiovascular events, evolocumab, LDL cholesterol, PCSK9 antibodies, safety.

1. Introduction

Despite the wide use of lipid modifying drugs, considerable cardiovascular mortality and morbidity remains. Hypercholesterolemia has a key role in the development and progression of atherosclerosis, and leads to cardiac heart disease. The primary target in the treatment of hypercholesterolemia is lowering LDL cholesterol optimally, which according to the National Cholesterol Education ATP III guidelines is <100 mg/dL (2.59 mmol/L). The medicines most commonly used initially to lower LDL cholesterol are the statins. If the statins are unsuccessful at achieving the 2.59 mmol level of LDL cholesterol, one approach is to increase the dose of the statin, but this also increases the likelihood of adverse effects with the statins. Another problem with increasing the dose of the statin is, although it further decreases the levels of LDL cholesterol, this is often not enough to reach optimal levels of LDL cholesterol.

An alternative approach, when statins do not lower LDL cholesterol optimally, is to add another LDL cholesterol lowering medicine to the statin. A new candidate for this is the monoclonal antibodies to proprotein convertase substilisin-kexin type 9 (PCSK9). PCSK9 has a key role in the intracellular degradation of the LDL receptor within the liver. In mice lacking *Pcsk9*, there are increased LDL receptors [1]. In humans, a mutation leading to the loss of function of PCSK9 is associated with reduced LDL cholesterol concentrations and risk of coronary heart disease [1]. Thus, human monoclonal antibodies that bind to inhibit PCSK9 would be predicted to reduce LDL cholesterol and cardiovascular events. Evolocumab and alirocumab are antibodies to PCSK9, and have been shown to markedly reduce LDL cholesterol levels and this suggests that these antibodies may be very useful in reducing cardiovascular outcomes in coronary heart disease. This evaluation is of two clinical trials purporting to show that these antibodies do reduce cardiovascular events; the first is with evolocumab (AMG 145; Section 2), Extensions of Open-Label Study of Long-Term Evaluation against LDL Cholesterol 1 (OSLER-1) and OSLER-2 [2]; the second is with alirocumab; Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modify-Therapy (ODYSSEY LONG TERM) [3].

2. Evolocumab

2.1 The story so far

Evolocumab alone at 105 or 140 mg, every 2 weeks for 12 weeks, was shown to reduce LDL cholesterol from a baseline of 3.7 mmol/l by ~30%, and increased HDL cholesterol by ~10% in MENDEL (Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL in Patients Currently Not Receiving Drug Therapy for Easing Lipid Levels) [4]. Subsequently, evolocumab 105 and 140 mg every 2 weeks, and 280 and 350 mg every 4 weeks was tested, in the presence of statin treatment, and shown to reduce LDL cholesterol from a baseline of 3.2 mmol/l by 50-60%, and to increase HDL cholesterol by ~5% in LAPLACE-TIMI 57 [5]. Other phase 2 trials showed that evolocumab was similar effective in subjects with heterozygous familial hypercholesterolemia (RUTHERFORD; The Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholestrolemia Disorder) [6] and in subjects who were statin-intolerant (GAUSS; The Goal Achievement after Utilizing an anti-PCSK antibody in Statin Intolerant Subjects) [7]. All of these phase 2 studies showed few adverse effects and good tolerance to evolocumab over 12 weeks. This led to Phase 3 studies which had similar findings.

2.2 OSLER extension [2]

OSLER-1 was the combination of five Phase 2 studies, and OSLER-2 of seven Phase 3 studies with evolocumab. After completion of these diverse OSLER trials, participants were allowed to enrol in the OSLER extension study, with provisos including not have had an adverse effect that had led to discontinuation previously, or having an unstable medical condition. Of the original participants, 4465 (74%) enrolled in the extension, and 2976 received evolocumab (140 mg/every 2 weeks or 420 mg/once a month, subcutaneously) and 1489 the local standard therapy.

At baseline, the groups were matched with a mean age of ~58 years, had similar percentages of males and females, and were predominantly White (86%). About 52% of participants had hypertension, ~23% family history of premature coronary artery disease, ~10% known familial hypercholesterolemia, ~33% metabolic syndrome, and ~14% diabetes. About 70% of participants were taking statins; 27% high intensity (atorvastatin, 40-80 mg; rosuvastatin 20-40 mg); 35% moderate intensity (atorvastatin, 10-20 mg; rosuvastatin, 5-10 mg; simvastatin, 20-40 mg).

The median follow-up was 11.1 months. In the OSLER extension, the LDL cholesterol levels settled after 12 weeks to ~1.16 mmol/l in the evolocumab group, compared to 3.12 mmol/l with standard therapy. Evolocumab also increased HDL cholesterol by 7%, reduced triglyceride levels by 13%, and reduced lipoprotein(a) levels by 26%.

A pre-specified exploratory outcome of the OSLER extension was the incidence of cardiovascular events. The number of cardiovascular events, after a follow-up of 11.1 months was low, and occurred in 29 of 2976 subjects in the evolocumab group (1.0%), which a was significantly lower percentage than the 31 of 1489 subjects in the standard care group (2.2%), P = 0.003.

There was no excess of serious adverse effects or overall adverse effects for evolocumab, compared to standard care, and this included aminotransferase and creatine kinase levels. Although there was a low incidence of neurocognitive events in the evolocumab group (0.9%), this was more frequent than in the placebo group. Injection site reactions occurred in 4.3% of subjects with evolocumab.

3. ALIROCUMAB

3.1 The story so far

Similar to evolocumab, alirocumab has been shown to lower LDL cholesterol alone or in the presence of a statin, and in subjects with heterozygous familial hypercholesterolemia. For example, in healthy volunteers, subcutanous alirocumab (REGN727/SAR236553) 50-250 mg alone reduced LDL cholesterol by 33-46% [8]. In subjects with primary hypercholesterolemia taking atorvastatin 80 mg, subcutanous alirocumab 150 mg every 2 weeks, reduced LDL cholesterol by 56% [9]. In subjects with familial hypercholesterolemia taking atorvastatin, alirocumab 50-150 mg reduced LDL cholesterol by 41-58% [8].

3.2 ODYSSEY LONG TERM [3]

ODESSEY LONG TERM was a randomised double-blind placebo controlled phase 3 trial of alirocumab. Subjects with heterozygous familial hypercholesterolemia or established coronary heart disease or coronary heart disease risk were eligible to enrol of they were receiving high dose statin therapy or statin therapy at the highest tolerable dose and had an LDL cholesterol level of 70mg at screening. A total of 2341 subjects were enrolled and were randomly assigned to receive either alirocumab (1553) or the placebo (788). Subjects continued with their statin therapy and received alirocumab 150mg or the placebo subcutaneously every two weeks for 78 weeks.

At baseline the two groups were matched, the mean age was 61 years with males in majority at ~62% and a study population that was ~93% White. Approximately 18% had heterozygous familial hypercholesterolemia, 69% established coronary heart disease, ~ 42% were at risk of coronary heart disease, ~34% had type 2 diabetes and ~21% were currently smokers. All but 2 subjects were on statin therapy, with ~47% on high dose statin.

The primary efficacy end point for ODESSEY LONG TERM was the change in LDL cholesterol levels from baseline to 24 weeks. At 24 weeks the mean LDL cholesterol level was ~1.24 mmol/L, and there was a reduction of 61% in the alirocumab group compared a gain of ~0.8% in the placebo group. Subjects with and without heterozygous familial hypercholesterolemia had similar changes in LDL cholesterol levels with alirocumab. In those who had higher LDL cholesterol levels at baseline, the percentage change from baseline to 24 weeks was smaller in both the alirocumab and placebo groups. Larger changes in mean secondary lipid variables occurred in the alirocumab group with HDL cholesterol increasing by 4%, fasting triglycerides decreasing by 16%, and lipoprotein(a) decreasing by 26%. The mean reductions between the baseline LDL cholesterol levels to 78 weeks were ~52% and ~4% in alirocumab and placebo groups, respectively.

Post-hoc analysis showed that the alirocumab group had lower rates of adjudicated major adverse cardiovascular events 1.7% (27 of 1550 subjects), compared to the placebo 3.3% (26 of 788 subjects); P = 0.02. With this small number of events, only non-fatal myocardial infarction was shown to be significantly lower with alirocumab (0.9%) compared with placebo (2.3%).

Similar adverse advents occurred between the alicrocumab and placebo groups and there was no difference in aminotransferase and creatine kinase levels between groups. Significantly, higher rates of myalgia 5.4% occurred with alirocumab than with placebo 2.9%. Neurocognitive events including amnesia, memory impairment, and confusional state were more common with alirocumab (1.2%) than placebo (0.5%), but these values were not significantly different. Injection site reactions occurred in 5.4% of subjects with alirocumab, which was not significantly different than the 2.9% with placebo.

4. Conclusions

Evolocumab and alirocumab have a marked ability to reduce the surrogate endpoint of LDL cholesterol, and this suggests that they may be very useful in reducing cardiovascular outcomes in coronary heart disease. Indeed, OSLER and ODYSSEY LONG TERM have shown that evolocumab and alirocumab probably have beneficial effects on cardiovascular outcomes. However, as these trials only had a small number of cardiovascular endpoints, and there are some safety concerns for evolocumab and alirocumab, we suggest that they are used sparingly and with caution until the results of the major outcomes trials with these antibodies are known.

5. Expert opinion

5.1 Potential of antibodies to PCSK9

The antibodies to PCSK9, evolocumab and alirocumab, cause a marked reduction in the levels of LDL cholesterol. The reduction of ~60% in LDL cholesterol with both evolocumab and alirocumab is greater than the reductions observed with either the statins or ezetimibe. At present, evolocumab and alirocumab are being considered for use as add on therapy in subjects with familial hypercholesterolemia, subjects who do not get an adequate reduction in LDL cholesterol with statins alone, and subjects who are intolerant of statins. Given the marked reduction in LDL cholesterol with evolocumab and alirocumab, it is conceivable that they will be considered for earlier use in the treatment hypercholesterolemia in the future. However, prior to any widespread use of the PCSK9 antibodies, their safety and cardiovascular outcomes need to be established.

5.2 Safety and cardiovascular outcomes with evolocumab

The neurocognitive adverse effects were higher with evolocumab than placebo in the OLSER extension, and may have been underestimated. Thus, as stated by the authors, one of the limitations to the OSLER extension was that subjects who had had adverse effects previously were excluded [2]. This is unfortunate, as some of the previous studies, from which the subjects for the OSLER extension were derived, had shown other adverse effects. Thus, in the phase III MENDEL-2 trial, four serious adverse effects occurred in the evolocumab group of 134 over the 12 week duration, whereas only one occurred in the placebo (n = 68) and ezetimibe groups (n = 70) [10]. The local investigators considered that two of these adverse effects were due to evolocumab; firstly, acute pancreatitis in a subject with a history of cholecystectomy, long-term alcohol intake, and concomitant use of valproate semisodium, and secondly, transaminase and creating kinase levels 8 times the normal upper limit, which returned to normal when the subject discontinued evolocumab [10]. In the longer 52 week phase III DESCARTES (Durable Effect of PCSK9 Antibody Compared with Placebo Study) trial, elevations of creatine kinase levels to more than 5 times the upper normal level occurred in 7 subjects (1.2%), compared to 0.3% subjects in placebo group, and of aminotransferase to more than 3 times the normal level occurred in 0.8% of subjects in evolocumab group (vs 0.1%, placebo group) [11].

The results collectively indicate that the incidence of adverse effects with evolocumab is low, and often too low to do meaningful statistics on. However, it should be noted that the number of subjects who have currently received evolocumab is relatively low and much larger and longer studies will be needed to pick up any rare, serious adverse effects of evolocumab, especially it they develop over time.

As the number of adverse cardiovascular events were low in the OSLER extension, it was not possible to ascertain which cardiovascular events (e.g. myocardial infarction) were reduced by evolocumab. Thus, a large clinical trial is needed to determine both the safety and cardiovascular effects of evolocumab. It is likely that the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 inhibition in Subjects with Elevated Risk) trial will provide this information [12]. FOURIER has enrolled 27,999 high risk subjects e.g. history of clinically evident cardiovascular disease at high risk for a recurrent event, into a double-blind comparison of evolocumab with placebo, in the presence of statin treatment [12]. The primary endpoints in FOURIER is the time to cardiovascular death, myocardial infarction, hospitalization of unstable angina, stroke, or coronary revascularization, whichever occurs first [12]. Unfortunately, FOURIER is not due for completion to end of 2017/start of 2018. It seems to us that evolocumab should not be registered or widely used in the population that are being enrolled in FOURIER, until this study has been completed.

In the OSLER extension, there was a population of subjects with familial hypercholesterolemia, who are at very high cardiovascular risk and most of these will be at a higher risk than the subjects in FOURIER. However, the number of cardiovascular events in the OSLER extension was low, and there was no subgroup analysis. Thus, it seems to us, that intensive safety and cardiovascular event monitoring with evolocumab should be a requirement of any registration of evolocumab in subjects with familial hypercholesterolemia.

5.3 ODYSSEY LONG TERM

The authors have summed up the limitations to the ODYSSEY LONG TERM study extremely well [3]. There are 3 limitations; firstly, the shortness of study for drug (alirocumab) that is going to be used in a chronic condition; secondly, the need to undertake further studies of any potential detrimental effects of alirocumab on neurocognition; and thirdly, the limitation of evaluating cardiovascular outcomes from low numbers of events [2]. These limitations will be answered by the ODYSSEY OUTCOMES trial, which is an evaluation of cardiovascular outcomes after an acute coronary syndrome during treatment with alirocumab [13]. ODYSSEY OUTCOMES is enrolling 18,000 subjects, who have previously been hospitalized for an acute myocardial infarction or unstable angina to alirocumab or placebo [13]. The primary endpoint is time to first occurrence of coronary heart disease, any non-fatal myocardial infarction and non-fatal ischemic stroke, or unstable angina requiring hospitalization [13]. The study is due to be completed at the start of 2018 [13].

In ODYSSEY LONG TERM, there were 18% of subjects with heterozygous familial hypercholesterolemia, and alirocumab had the same ability to low LDL cholesterol in these, as in the

other subjects [3]. However, probably because of the small number of cardiovascular endpoints in the trial, no subgroup analysis of this for the familial hypercholesterolemia subjects was reported. Thus, as with evolocumab, intensive safety and cardiovascular event monitoring with alirocumab in heterozygous familial hypercholesterolemia should be a requirement of any registration of evolocumab.

5.4 HDL cholesterol, triglycerides and lipoprotein(a)

Low levels of HDL cholesterol, and high levels of triglycerides and lipoprotein(a) are all risk factors for cardiovascular disease in their own right. Both evolocumab and alirocumab increase the levels of HDL cholesterol and decreases the levels of triglycerides and lipoprotein(a), which are beneficial changes in these surrogate endpoints in subjects with cardiovascular disease. However, the mechanism/s of these effects is not clear to us; are they a consequence of lowering the LDL cholesterol? Or are other mechanisms, perhaps not related to PCSK9, involved in this? As these are beneficial changes, it would be of interest to have the mechanism clarified.

5.5 Statins, PCSK9 inhibitors, and ezetimibe

It was mentioned in the study by Koren et al, without reference, that statin use up-regulates PCSK9 levels [10]. One possible implication of this is that higher levels of PCSK9 antibodies may be needed to cause the same lowering of LDL cholesterol in the presence, than in the absence, of a statin, and this needs to be tested long-term.

At present, the drug most commonly added on to statins, when statins alone are considered to be not effective enough at reducing LDL cholesterol, is ezetimibe. However, in a study including a comparison of ezetimibe 10 mg to evolocumab 140 mg as add on to atorvastatin 10 and 80 mg, evolocumab showed a greater ability than ezetimibe to reduce LDL cholesterol [14].

The PCSK9 inhibitors have a greater ability to reduce LDL cholesterol than statins. Thus, in subjects with primary hypercholesterolemia on atorvastatin 10 mg, increasing the dose of atorvastatin to 80 mg decreased LDL cholesterol by 17%, whereas adding alirocumab 150 mg decreased LDL cholesterol by 66% [15]. Thus, in the future, as PCSK9 inhibitors have a greater effect on LDL cholesterol than high-dose statins, they may be considered for treatment alone, especially in subjects who are statin intolerant.

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* Early paper showing marked reduction in LDL cholesterol with evolocumab

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